Clinical Case Report

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Adult-onset hypophosphatemic osteomalacia associated with Sjogren syndrome

Clinical case report

Guohua Shen, MD, PhD[a], Yuwei Zhang, MD[b], Shuang Hu, MD[a], Bin Liu, MD[a], Anren Kuang, MD[a,*]

Abstract

Rationale: Hypophosphatemic osteomalacia (HO) is a metabolic bone disease, exhibiting different etiologies such as genetic mutation, tumor induction, dysimmunity, or renal disease. Sjogren's syndrome (SS) is a connective tissue disorder commonly involving exocrine glands; however kidney involvement is also encountered, leading to abnormal phosphorus metabolism, even HO.

Patient concerns: A 47-year-old female patient presented progressively worsening pain in the chest wall, back and bilateral lower extremities as well as muscle weakness was referred to our department.

Diagnoses, interventions and outcomes: Due to the laboratory test results, radiographic findings and pathologic results, she was diagnosed with adult-onset HO associated with SS. She was then treated with alkalinization, steroids, neutral phosphate, calcium supplements together with activated vitamin D. So far, she recovered uneventfully with relieved pain and increased serum phosphorus level.

Lessons: HO may be secondary to renal tubular acidosis of SS patients, and it might be a diagnostic challenge when the kidney involvement in SS is latent and precede the typical sicca symptoms.

Abbreviations: ALP = alkaline phosphatase, CT = computed tomography, ^{18}F-FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, HO = hypophosphatemic osteomalacia, SS = Sjogren syndrome, TIO = tumor-induced osteomalacia.

Keywords: hypophosphatemic osteomalacia, renal tubular acidosis, Sjogren syndrome

1. Introduction

Hypophosphatemia can cause an inadequate mineralization of the bone matrix, subsequently softening the bone and leading to osteomalacia.[1] Hypophosphatemic osteomalacia (HO) is a metabolic bone disease, exhibiting different etiologies such as genetic mutation, tumor induction, altered immunity, or renal disease.[2] Sjogren syndrome (SS) is a connective tissue disorder commonly involving exocrine glands; however, kidney involvement is also encountered.[3] Renal tubular acidosis caused by tubulointerstitial nephritis might lead to abnormal phosphorus metabolism, even HO.[4] Patients with HO usually present with clinical findings of bone pain, muscle weakness, and occasionally pathological fracture, with biochemical findings of serum hypophosphatemia, reduced active vitamin concentration, and increased alkaline phosphatase (ALP). For further etiological investigation, a wide variety of clinical, laboratory, and radiographic examinations were performed, which might delay the diagnosis. Here, we report one case showing multiple bone fractures due to HO in a patient with SS.

2. Case report

A 47-year-old female patient presented progressively worsening pain in the chest wall, back, and bilateral lower extremities as well as muscle weakness. She did not have a family history of bone disease or fractures. Physical examination was unremarkable excluding bone and muscular abnormalities. Bone scintigraphy using technetium-99m methylenediphosphate showed increased uptake in the shoulder, multiple ribs, thoracic and lumbar spines, bilateral sacroiliac joints, left ilium, and left foot (Fig. 1). Plain radiographs revealed osteoporosis change of thoracic and lumbar spine as well as compression change of several spines, consistent with findings of magnetic resonance imaging and computed tomography (CT) (Fig. 1). Decreased bone mass was presented in the lumbar spine (T-score: −3.4), femoral neck (T-score: −3.1), and hip (T-score: −3.5).

Main laboratory data are shown in Table 1. She demonstrated hypophosphatemia, hypokalemia, hypourice-

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[a] Department of Nuclear Medicine, West China Hospital of Sichuan University, [b] Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China.

[*] Correspondence: Anren Kuang, Department of Nuclear Medicine, West China Hospital of Sichuan University, No. 37 Guoxue Alley, Chengdu, Sichuan 610041, People's Republic of China (e-mail: kuanganren@263.net).

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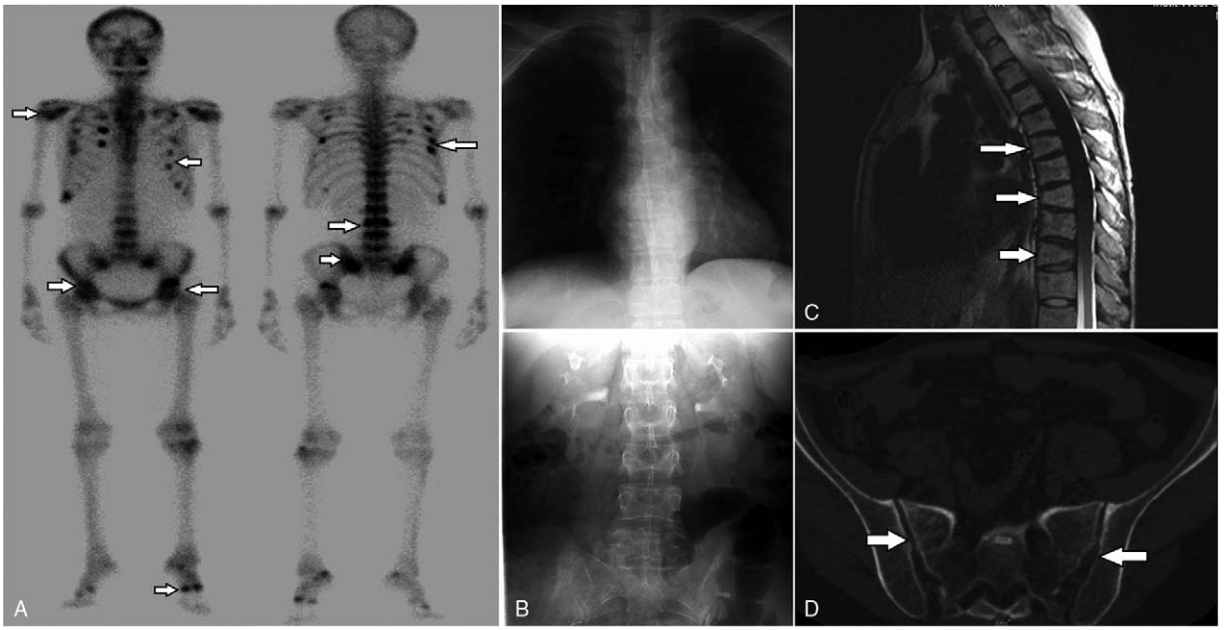

Figure 1. (A) whole body bone scintigraphy showed multiple foci of increased radiotracer uptake in the shoulder, multiple ribs, thoracic and lumbar spines, bilateral sacroiliac joints, left ilium, and left foot (arrow). (B) Plain radiographs revealed osteoporosis change of thoracic and lumbar spine as well as compression change of several spine. (C) MRI demonstrated osteoporosis and compression change of several thoracic spines (arrow). (D) CT showed degenerative changes and low bone density in the bilateral sacroiliac joints (arrow). CT = computed tomography, MRI = magnetic resonance imaging.

mia, elevated level of ALP, C-telopeptides and chloride, and decreased carbon dioxide combining power. The urinalysis revealed a high pH value, increased level of potassium, and decreased level of specific gravity, chlorine, and phosphate. Persistent glycosuria and proteinuria were repeatedly found, despite normal HbA1c and plasma glucose level. Other laboratory test results including thyroid function test, serum parathyroid hormone, 25-hydroxyvitamin D, and protein electrophoresis were within normal range. In addition, all of serum tumor markers were negative. Due to limited technique, we cannot determine the level of serum fibroblast growth factor 23.

With the clinical diagnosis of HO, fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and technetium-99m octreotide (^{99m}Tc-OCT) scintigraphy were performed to confirm whether the occult causative tumor exist. However, the results of these 2 tests were negative except that mild uptake in the seventh rib was found on PET/CT, which identified no evidence of a neoplastic lesion potentially responsible for HO (Fig. 2). The immunological examination showed elevated level of serum IgG, IgM, and IgA, as well as positive antinuclear antibody, anti-SSA antibody, and rheumatic factor. Subsequently, Schirmer test was abnormal and lip biopsy supported the diagnosis of SS (Fig. 3). Eventually, this patient was diagnosed with HO secondary to SS, and she was then treated with alkalinization (citrate 4 g/day and potassium citrate 3 g/day for 2 weeks), steroids (prednisone 20 mg/day for 1 month, 10 mg/day for 4 months), neutral phosphate (1.0 g/day for 5 months), calcium supplements (600 mg/day for 5 months), and together with activated vitamin D (0.5 g/day for 5 months). So far, she recovered uneventfully with relieved pain and increased serum phosphorus level. This case report was approved by the ethics committee of West China Hospital of Sichuan University, Chengdu, China, and the written informed consent was obtained.

3. Discussion

HO is a metabolic bone disorder characterized by abnormal phosphorus metabolism in bone mineralization. In these disorders, phosphatonins (phosphaturic hormones) inhibit renal tubular reabsorption of phosphate and reduce serum 1, 25-dihydroxyvitamin D level by mediating the several enzymes associated with vitamin D metabolism.[5–8] In clinical practice, this disorder cannot be only induced by phosphaturic mesenchymal tumor,[9,10] but also secondary to SS[4,11,12] or hyperparathyroidism,[13] even related to the adefovir therapy.[2,14] Although the clinical symptoms of HO are unspecific or noncharacteristic, it is very important and valuable to reveal etiological cause of this disorder to provide appropriate therapy.

As the most representative disorder, tumor-induced osteomalacia (TIO) is regarded as a paraneoplastic disorder of phosphaturic mesenchymal tumor. Most of these causative neoplasms are benign, presented with small size and slow growth rate and commonly located in peculiar or atypical sites so that their localization remains a challenge.[15,16]^{18}F-FDG PET/CT, ^{99m}Tc-OCT scintigraphy, and ^{68}Ga DOTATATE PET/CT played a considerable role in revealing TIO-associated tumors.[17–19] For these patients with TIO, complete surgical resection of causative tumors is the definitive treatment.

SS syndrome is an autoimmune disorder commonly involving exocrine glands including lacrimal and salivary glands, occasionally involving nonexocrine organs such as lung and kidney.[20] Fanconi syndrome is a rare kidney manifestation in Sjögren syndrome, diagnosed by renal tubular acidosis along with glycosuria or proteinuria.[21] Although the bone biopsy was not

Table 1

Resultsof laboratory tests.

Laboratory test	Reference range	Case	
Complete blood count			
ESR, mm/h	<26	65.0	↑
Red cell, $\times 10^{12}$/L	3.8–5.1	4.1	
Hemoglobin, g/L	115–150	117	
Platelet count, $\times 10^{9}$/L	100–300	121	
White cell, $\times 10^{9}$/L	3.5–9.5	3.6	
Serum characteristics			
Aspartate aminotransferase, IU/L	<35	40	↑
Alanine aminotransferase, IU/L	<40	36	
Glucose, mmol/L	3.9–5.9	4.94	
Uric acid, μmol/L	160–380	103	↓
ALP, IU/L	35–100	560	↑
B-ALP, μg/L	11.4–24.6	102.71	↑
C-telopeptides, ng/L	0.299–0.573	1.260	↑
Phosphate, mmol/L	0.81–1.45	0.65	↓
Calcium, mmol/L	2.1–2.7	2.29	
Chlorine, mmol/L	99.0–110	117.0	↑
Potassium, mmol/L	3.5–5.3	3.30	↓
Carbon dioxide combining power, mmol/L	18.0–28.0	16.9	↓
HbA1c, %	4.5–6.1	4.7	
Urinalysis			
pH	4.60–8.00	8.50	↑
Specific gravity	1.010–1.025	1.004	↓
Urine glucose, mmol/L	–	8.3 (2+)	+
Urine protein, g/L	–	1.5 (2+)	+
Urine potassium, mmol/24 h	40–80	85.35	↑
Urine chlorine, mmol/24 h	140–250	132.0	↓
Urine phosphate, mmol/24 h	22–48	16.07	↓
Immune testing			
IgG, g/L	8.00–15.50	25.4	↑
IgM, mg/L	700–2200	7910.0	↑
IgA, mg/L	836–2900	3920.0	↑
ANA	–	+(1:100)	+
anti-SSA	–	+	+
RF, IU/mL	<20.0	22.90	↑
Other index			
PTH, pmol/L	1.60–6.90	2.59	
25-Hydroxyvitamin D, nmol/L	47.7–144	51.03	
Thyroid function*	–	–	
Tumor makers*	–	–	
Protein electrophoresis*	–	–	

ALP = alkaline phosphatase, ANA = antinuclear antibody, anti-SSA = anti-Sjoigren syndrome A antibody, B-ALP = bone specific alkaline phosphatase, ESR = erythrocyte sedimentation rate, HbA1c = glycosylated hemoglobin-type A1c, PTH = parathyroid hormone, RF = rheumatic factor.

* The results of thyroid function, tumor makers, and protein electrophoresis were within normal range; ESR, ALP, B-ALP, PTH, HbA1c, ANA, anti-SSA, RF.

performed for our case, the diagnosis of HO was supported by the biochemical characteristics (serum hypophosphatemia, increased ALP) and imaging findings (osteoporosis, multiple fractures). The occurrence of HO in SS is due to the kidney involvement, including tubulointerstitial nephritis and tubular dysfunction.[4] It is reported that most of SS patients demonstrated distal renal tubular acidosis, and abnormal phosphorus metabolism was usually related to the distal renal tubular acidosis while proximal renal tubular acidosis, just like Fanconi syndrome, is rarely encountered in SS patients.[4,22] Another study demonstrated that the pathological phenotype of Fanconi syndrome might occur in not only distal but also proximal tubular dysfunction.[23] In our case, the proteinuria and normoglycemic glycosuria indicated the presence Fanconi syndrome, meanwhile, our patient also showed some characteristics of distal tubular dysfunction such as alkalized urine. Hypophosphatemia was a result of long-term mixed distal and proximal renal tubular acidosis. In addition, HO is a very rare syndrome associated in 5% of cases with tertiary hyperparathyroidism due to long-term therapy with phosphorus and vitamin D.[24] Adefovir, as an antiviral agent, is widely used in the management of patients with chronic hepatitis B. However, there is an increasing number of reports demonstrating that long-term use of adefovir can induce nephrotoxicity, even at a low dose.[2,11,14] Quite evidently, adefovir therapy is not a reasonable explanation for our case.

In conclusion, it is of importance to identify the potential cause of HO to choose an appropriate treatment. This disorder may be secondary to renal tubular acidosis of SS patients, and it might be a diagnostic challenge when the kidney involvement in SS is latent and precede the typical sicca symptoms.

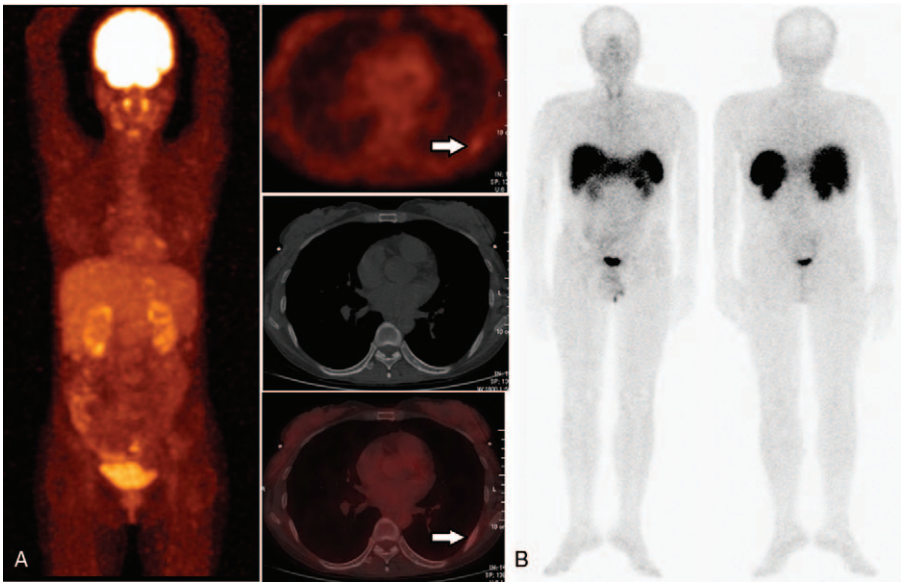

Figure 2. ^{18}F-FDG PET/CT only showed a mild uptake in the seventh rib which might be an insufficiency fracture (arrow) while the result of ^{99m}Tc-OCT was negative. ^{18}F-FDG PET/CT = fluorodeoxyglucose positron emission tomography/computed tomography, ^{99m}Tc-OCT = technetium-99m octreotide.

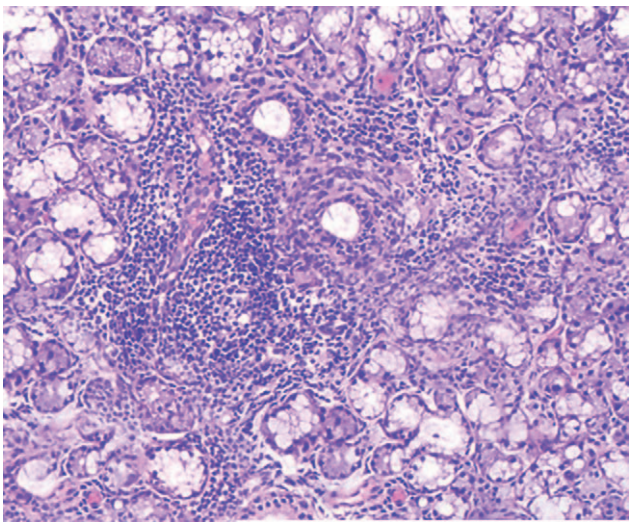

Figure 3. Lip biopsy showed plasma cell infiltration around the salivary gland ducts, compatible with Sjögren syndrome.

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